Self-medication of a single headache episode with ketoprofen, ibuprofen or placebo, home-monitored with an electronic patient diary

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- 1 The objective of this study was to investigate the efficacy of home-medicated non-steroidal anti-inflammatory (NSAID) analgesics, using an electronic patient diary. Single doses of ketoprofen 25 mg and ketoprofen 50 mg were compared with ibuprofen 200 mg and placebo in the treatment of a single occasion of episodic tension-type headache, using a double-blind, randomized, parallel group design.
- 2 A total of 166 patients with headache compatible with episodic tension-type headache and no refractory headaches or contraindications to NSAIDs were contacted by advertisements and selected by questionnaires. Patients performed the study at home, using an electronic diary for headache assessment, with a form to allow comments and corrections. Visual analogue scales (VAS 10 cm) of headache severity, five-item headache relief rating (HRR) scales, and time of intake of 'escape' analgesics were scored regularly, for 4 h following intake of trial medication.
- 3 VAS-scores ($n=1407$) and HRRs ($n=452$) were returned by 159 patients. Of these scores, 1.5% were inadvertently omitted from the electronic diary or modified on the comment forms.
- 4 Headache (VAS and HRR) improved more with all three NSAIDs than with placebo, although the effect of ibuprofen was significant for HRR only. After 2 and 4 h respectively, the reduction in VAS-ratios was 17 and 19% with placebo, 18 and 53% with ibuprofen 200 mg, 41 and 61% with ketoprofen 25 mg, and 47 and 59% with ketoprofen 50 mg. After 4 h, headache improved strongly (highest HRR) in 18% of patients on placebo, 39% on ibuprofen 200 mg, 62% on ketoprofen 25 mg, and 55% on ketoprofen 50 mg. Headache disappeared completely (VAS-score=0) in one patient (3%) with placebo (after 180 min), 10% with ibuprofen 200 mg (average 211 min), 18% with ketoprofen 25 mg (159 min), and 28% with ketoprofen 50 mg (146 min).
- 5 The effects of ketoprofen 50 mg were more pronounced than those of ibuprofen 200 mg, which seemed to start later. Ketoprofen 25 mg and 50 mg were very similar, suggesting a maximal effect of the lower dose. Mild to moderate adverse events were reported by 9% of the patients, half of which occurred with ketoprofen 50 mg. Treatment of headache with ketoprofen can start with 25 mg, and possibly less.
- 6 Although a direct comparative study would be necessary to determine the relative benefits of the novel electronic patient diaries over traditional paper-and-pencil methods, this study has shown the usefulness of this newer technique to detect differences in efficacy between low doses of analgesics under ambulant conditions, with very limited loss of data. Electronic patient

diaries appear to be an important new attribute for the efficacy assessment of self-medicated drugs.

Keywords clinical trials electronic diaries headache non-steroid anti-inflammatory drugs self-medication

Introduction

Ketoprofen belongs to the class of arylpropionic acid derivatives. It is a strong inhibitor of prostaglandin synthesis. It is widely used in rheumatology [1], and has a strong analgesic effect in dental pain [2, 3], dysmenorrhoea [4], postpartum pain [5, 6], post-operative pain [6–8] and cancer pain [6, 9]. Episodic tension-type headache (also called 'ordinary' or muscle contraction headache) [10] is one of the most common causes of pain [11]. It has been advocated as a model to assess mild analgesic drugs [12]. Several arylpropionic acid derivatives, such as naproxen [13], ibuprofen [14, 15], and pirofen [16] have been shown to be safe and efficacious for the treatment of episodic tension-type headache. Ibuprofen is registered for self-medication for headache in several countries. Ketoprofen has recently also been registered for self-medication [17], but its efficacy in tension-type headache is undetermined.

The assessment of analgesics in headache poses several difficulties [18]. Although trial procedures can be intensively monitored at research institutions, this entails a self-selection by the patient of the moment to go to the institute with headache. This decision will be influenced by matters of convenience and by pain intensity, which in turn can be altered during transportation to the institution, and by the unusual trial circumstances. Hence, the ingestion of analgesics in in-patient studies may not be truly representative of the spontaneous intake of pain-killers for 'ordinary' headaches. Ambulant studies require full cooperation by the patient, which may be less reliable particularly when headache is severe. The use of an electronic patient diary may improve the reliability of home-collected data, allowing a more precise evaluation of drugs in ambulant situations, such as during chronic treatment [19]. The present study used electronic diaries to home-monitor the efficacy of ketoprofen (25 mg and 50 mg), compared with ibuprofen 200 mg and placebo, during self-medication of a single occasion of episodic tension-type headache.

Methods

Subjects

Volunteers of at least 18 years of age, with regular headaches of at least four times a month, but no more than three times a week and no migraine, were approached by advertisements in regional newspapers and on local cable television. Responders were provided

with a questionnaire, designed to elucidate the regular features of the headache and concomitant complaints, and contra-indications for the use of non-steroidal anti-inflammatory drugs (NSAIDs). If necessary, further information was obtained by interview. For selection, the headache characteristics had to comply with the criteria of the International Headache Society (IHS) for episodic tension-type headache (with or without disorder of pericranial muscles, IHS 2.1.1 or 2.1.2) [10]. No medical examination was performed, since the study was designed to mimic the entirely unsupervised intake of 'over-the-counter'-analgesics for 'ordinary' headache. Therefore, the IHS criterion for episodic tension-type headache that physical- and neurological examinations do not suggest any other relevant disorder was not met. In the 2 months prior to the participation, subjects were required to have suffered from between four and twenty-four occasions of headache of at least moderate severity, usually lasting at least 3 h and usually responsive to self-medicated analgesics. Patients with criteria conforming to unspecified tension-type headache (IHS 2.3) that otherwise satisfied the study criteria were also included, if they usually responded satisfactorily to analgesics. Patients with features suggestive of other (concomitant) headache types were excluded, notably migraine (IHS 1), chronic tension-type headache (IHS 2.2) or cluster-type headaches (IHS 3). Subjects with health hazards for the use of NSAIDs were also excluded. All subjects participated after full written informed consent. The study was approved by the Medical Ethics Committee of Leiden University Hospital.

Study design and medication

This study was a single dose, double-blind, randomized, parallel group, placebo-controlled efficacy study of ketoprofen 25 mg, ketoprofen 50 mg and ibuprofen 200 mg, in the treatment of a single headache occasion, home-monitored with an electronic patient diary. Subjects were allowed to use their personal analgesic medication as an 'escape', if headache relief was insufficient after at least 2 h following ingestion of trial medication.

Electronic patient diary

After selection, patients were invited to the institute in groups of 2–10 subjects, for thorough instructions about the study design, and to practice with the electronic patient diary. The electronic patient diary

(MiniDoc AB, Uppsala, Sweden) is specifically designed for out-patient clinical trials [19]. The apparatus is essentially a portable computer with a large LCD-screen and four push-buttons, which are pre-programmed according to the study protocol. The main features of the programme were 10 cm visual analogue scales (VAS) of headache intensity and five item headache relief ratings (HRR). In addition, the ingestion of personal ('escape') analgesic medication and its time could be indicated, either upon request at scheduled timepoints, or spontaneously in between. The different steps of the programme were evoked in a scheduled order, by means of an alarm with fixed time intervals. Previously entered responses were not displayed. Any omitted information was requested again at the next scheduled time point. The programme could not be interrupted after the start, except to indicate the ingestion of 'escape' analgesics. The entered data could not be changed afterwards. Since there was no opportunity for corrections, patients were provided with a comment form that contained important study guidelines and visual analogue lines, giving the opportunity to change data that were considered to have been incorrectly entered into the diary. Patients were clearly instructed that only obvious errors should be corrected immediately after these were made.

Headache assessment

Subjects were instructed to switch on the electronic patient diary, during the first occasion of episodic tension-type headache to occur within the first month after the screening period, when the headache reached at least moderate severity. The diary programme initially checked whether the headache was at least moderately severe, indicated by VAS-score of 25% or more of the maximal headache level. If so, the patient was instructed to take the trial medication. The diary then prompted for entry of the next VAS-score with loud bleeps at 15, 30, 45, 60, 90, 120, 180 and 240 min. In addition, a five-item Headache Relief Rating-(HRR)-score (0 strong worsening—1 slight worsening—2 no change—3 slight improvement—4 strong improvement) was obtained at 120, 180 and 240 min. Two hours or more after intake of the test drug, the patients were allowed to take their own analgesic medication. If so, they were instructed to switch on the electronic diary, which then inquired about the time of ingestion of 'escape' analgesics, and the VAS- and HRR-scores immediately before ingestion. The programme also inquired at 180 and 240 min about the intermediary use of such analgesics. The study was terminated after 'escape' analgesics was taken, or after 4 h. When the trial material was returned, patients were asked about their experience with the diary programme, the effect of trial medication, the use of 'escape' analgesics, and adverse events. The data retrieved from the diary and the corrections on the comment form were compared with the overview provided by the patient. Clear discrepancies were investigated.

Statistical analysis

The number of subjects in each treatment group (forty) was based on comparable parallel-group trials of arylpropionic acid derivatives in episodic tension-type headache, where 35–50 patients per treatment group sufficed to detect a significant analgesic effect [12–15]. Studies of ketoprofen 25 mg in pain other than headache showed significant effects in 14–50 patients per group [2–7]. Statistical analyses were performed on the as per protocol population. VAS headache scores and HRR-scores were analysed by a procedure analogous to a repeated measures ANOVA, adequately accounting for missing data (SAS PROC MIXED, SAS for Windows V6.07, SAS Institute Inc., Cary, NC). The study was designed to produce a final VAS- or Headache Relief score prior to ingestion of 'escape' medication (if applicable), but all datapoints expected thereafter were considered missing. VAS-scores were analysed as raw scores (9 in total) from 0 to 240 min. VAS-scores were significantly related to the values at baseline, shown by covariance analysis ($P < 0.0001$). Hence, VAS-scores were also analysed as the ratio of scores relative to the pre-value ($t = 0$ min) (8 in total) from 15 to 240 min. Pairwise differences between treatments were assessed using contrasts on average treatment effects. The following categorical variables were analysed using Fisher's exact test: intake of escape medication, intake of escape medication immediately after 120 min, headache free status at 240 min (VAS = 0), strong headache relief (HRR = 4) at 240 min, presence of unspecified tension-type headache (IHS 2.3), and adverse events. Contrasts between treatments were only examined in case of overall significant differences (set at 5%). Significance levels for contrasts between groups were set at 1% to account for multiple comparisons. Results are reported as averages with 99% confidence intervals, or with P values in case of Fisher's exact test.

Results

Subjects and data

A total of 303 individuals responded to the advertisements. Two hundred and forty-eight questionnaires were returned. Eighty subjects were rejected: 48 for suspected (concomitant) migraine; 11 for too frequent or chronic headache; 6 for absent relief from self-medicated analgesics; 4 for contra-indications to the use of NSAIDs; 2 for intercurrent illness; 1 for suspected inability to operate the electronic diary; and 8 for mixed reasons.

Of the 168 eligible subjects, 140 patients matched the criteria for episodic tension-type headache (IHS 2.1.1 or 2.1.2) and 28 for unspecified tension type-headache (IHS 2.3). Two subjects refused further participation; 41 received placebo, 42 ibuprofen 200 mg, 41 ketoprofen 25 mg, and 42 ketoprofen 50 mg. Of the 166 participants, three subjects took trial medication without entering any data into the electronic diary, and four subjects withdrew consent and returned the unused trial material.

Of the remaining 159 subjects who returned evaluable data, 39 patients received placebo, 40 ibuprofen 200 mg, 39 ketoprofen 25 mg, and 40 ketoprofen 50 mg. Only minor deviations from protocol were encountered. Eleven subjects made changes on the comment form, which were analysed instead of the data originally entered into the electronic diary. In this way, 10/1407 VAS-scores (0.7%) and 9/452 HRR-scores (2%) were corrected; five HRR-scores (1.1%) and three VAS-score (0.2%) were lost. Overall, 1.5% of the analysed data were lost or different from the original diary entries.

There were no differences in demographic data or headache characteristics at baseline (Table 1). More women participated in the study than men (109 *vs* 50).

Efficacy

Pain intensity scores (visual analogue scales) The development of the raw VAS-scores over the entire 4 h period is shown in Table 2. Both ketoprofen doses differed significantly from placebo, but the differences between the three active treatment groups were not statistically significant. The treatment effects became more pronounced, if the baseline VAS-scores were taken into account. Figure 1 shows the VAS-scores as ratios of the pre-treatment value. Ketoprofen 25 mg and 50 mg reduced VAS-ratios significantly more than placebo (average difference with placebo (99% confidence interval) over 4 h: 20% (1, 38%) and 22% (4, 41%), respectively). The higher dose was also significantly more effective than ibuprofen 200 mg (difference 19%

Figure 1 Average VAS-ratios, relative to the baseline VAS-score, during treatment with placebo (●), ibuprofen 200 mg (◆), ketoprofen 25 mg (▼) and ketoprofen 50 mg (■). Open symbols and dashed lines represent averages corrected for missing values.

(1, 37%)). The average difference between ibuprofen and placebo was not statistically significant (3% (–2, 34%)).

Only one patient from the placebo group (3%) became free of headache (defined as a VAS-score of 0), after 3 h. In the ibuprofen 200 mg group, four patients (10%) became headache-free after an average of 211 min (range 181–242 min), compared with seven patients (18%) in the ketoprofen 25 mg group (159 (60–242) min), and 11 (28%) in the ketoprofen 50 mg group (146 (30–241) min). More patients lost their headache with ketoprofen 50 mg than with placebo

Table 1 Demographic variables and baseline headache data

	Placebo	Ibuprofen 200 mg	Ketoprofen 25 mg	Ketoprofen 50 mg
Number (n)	39	41	39	40
Age (years, mean, range)	39.1 (21–68)	38.8 (21–64)	38.2 (23–73)	40.4 (23–70)
Gender (M/F)	16/23	14/27	10/29	10/30
Symptoms compatible with unspecified tension-type headache (IHS 2.3) (number of subjects)	7	6	9	5
Headache episodes in prior 2 months (n, mean, range)	13.6 (4–28)	14.1 (5–28)	13.7 (4–28)	14.7 (6–28)
Baseline headache severity (VAS-score, mean, range)	0.51 (0.26–0.86)	0.45 (0.26–0.96)	0.48 (0.26–0.86)	0.49 (0.26–0.83)

Table 2 Average changes in headache severity (raw VAS-scores) over 4 h

Treatment	Placebo	Ibuprofen 200 mg	Ketoprofen 25 mg	Ketoprofen 50 mg
Average 4 h scores	0.46	0.38	0.35	0.35
Placebo	–	–0.08 (–0.17, 0.01)	–0.11 (–0.20, –0.02)	–0.11 (–0.20, –0.02)
Ibuprofen 200 mg	–	–	–0.03 (–0.12, 0.06)	–0.03 (–0.12, 0.06)
Ketoprofen 25 mg	–	–	–	–0.00 (–0.09, 0.09)

All values except in the top row show differences between average raw VAS-scores, of left column *vs* top row, presented as mean with 99% confidence interval.

($P=0.003$). There were non-significant differences between placebo and ketoprofen 25 mg ($P=0.056$) and between ketoprofen 50 mg and ibuprofen 200 mg ($P=0.049$).

Headache relief ratings The average HRR-scores are shown in Figure 2. Table 3 shows the differences between the four treatment groups. All NSAIDs gave significantly more pain relief than placebo. After 4 h, there was a strong improvement of headache (maximum HRR-score of 4) in seven patients (18%) on placebo, 16 (39%) on ibuprofen 200 mg, 24 (62%) on ketoprofen 25 mg, and 22 (55%) on ketoprofen 50 mg. Strong improvement occurred more often with ketoprofen 25 mg ($P<0.001$) and ketoprofen 50 mg ($P=0.001$) than with placebo, but the difference between placebo and ibuprofen 200 mg failed to reach statistical significance ($P=0.049$).

Intake of 'escape' analgesics Figure 3 shows the numbers of patients resorting to 'escape' analgesics, and the time of intake. Six patients on placebo (15%) used 'escape' medication immediately after this was allowed, as opposed to one patient on ibuprofen 200 mg (2%) and none on either dose of ketoprofen. Immediate resort to 'escape' analgesics occurred (non-significantly) more often during treatment with placebo than with either ketoprofen 25 mg ($P=0.025$), ketoprofen 50 mg ($P=0.012$) or ibuprofen 200 mg ($P=0.054$).

Figure 2 Average headache relief-ratings during treatment with placebo (●), ibuprofen 200 mg (■), ketoprofen 25 mg (▼) and ketoprofen 50 mg (▲). Open symbols and dashed lines represent averages corrected for missing values.

Table 3 Average changes in average headache relief (HRR-scores) over 4 h

Treatment	Placebo	Ibuprofen 200 mg	Ketoprofen 25 mg	Ketoprofen 50 mg
Average 4 h scores	2.43	2.95	3.21	3.25
Placebo	—	0.52 (0.00, 1.03)	0.78 (0.25, 1.30)	0.82 (0.30, 1.34)
Ibuprofen 200 mg	—	—	0.26 (−0.25, 0.78)	0.31 (−0.20, 0.82)
Ketoprofen 25 mg	—	—	—	0.04 (−0.47, 0.56)

All values except in the top row show differences between average Headache Relief-ratings of left column *vs* top row, presented as mean with 99% confidence interval.

Figure 3 Percentage of patients not taking 'escape' analgesics during treatment with placebo (●), ibuprofen 200 mg (■), ketoprofen 25 mg (▼) and ketoprofen 50 mg (▲).

Adverse events

Fourteen adverse events were reported. Seven occurred during treatment with ketoprofen 50 mg: two cases of mild gastrointestinal discomfort, three of restlessness, one of mild itching, and one case of moderate angioneurotic oedema responding to oral anti-histamine treatment. Adverse events did not occur significantly more often ($P>0.15$) with ketoprofen 50 mg than with the other treatments (two with ketoprofen 25 mg group, three with ibuprofen 200 mg and two with placebo; mostly mild to moderate self-limiting gastrointestinal complaints or 'unusual' headache).

Discussion

The present study was designed to approach the situation where an 'over-the-counter' analgesic is occasionally taken for 'ordinary' headache. Both the selection of patients and the methods of evaluation were adapted to this every-day situation. Subjects were recruited by advertisement through local media, rather than through general practitioners, neurologists or headache clinics. Efforts were made to exclude subjects with refractory headache types. Patients performed the study at home, using an electronic patient diary to improve the quality of the assessments. Data were not

displayed and could not be changed after entry into the diary, to prevent *post-hoc* entrance or modification and to minimise carry-over effects from previous scores. Patients were thoroughly instructed, and a patient information- and correction form was provided with the electronic diary. Although this to some extent foils the essence of electronic patient diaries, many patients wanted the opportunity to make remarks or modifications during the trial, although only 19 of 159 subjects actually used it. Thus, no more than 1.5% of the data were lost or modified. It is therefore very unlikely that an analysis of the unaltered electronic diary entries would have yielded different results. This suggests that it is unnecessary to backup electronic patient diaries with paper-and-pencil methods. The large majority of the patients had no difficulties with the use of the electronic patient diary, and there generally seemed to be a good agreement between the entered data and the overall patient assessment. Furthermore, this study clearly showed the feasibility of the electronic patient diary to demonstrate the efficacy of low doses of analgesics under ambulant conditions, which is also an indication of the reliability of the methodology in trials such as these. However, the relative advantages of the electronic patient diaries compared with traditional paper-and-pencil methods cannot be determined from this study.

All three NSAID-treatments improved headache, relative to placebo. The effects of ibuprofen were less clear than the effects of ketoprofen, and statistically significant only for average headache relief. If the overall VAS-response over 4 h was corrected for the baseline headache severity, ketoprofen 50 mg was more effective than ibuprofen. The difference in efficacy between ibuprofen and ketoprofen seemed to be largely related to a later onset of action of ibuprofen. The time-profiles of the VAS-scores indicated that the reduction in pain severity with ibuprofen was very similar to placebo up to 2 h, when ketoprofen already provided noticeable pain-relief. After 4 h however, all NSAIDs were equally effective. This difference in onset of action is also suggested in the subgroups of patients who experienced complete relief from headache. This occurred approximately 1 h sooner after ketoprofen than after ibuprofen. This may be related to differences in $t_{\max}$, which are 90 and 45 min respectively, according to the product information.

The effects of ibuprofen 200 mg on headache, which is registered in this dose as a self-medication analgesic for this indication, were marginally demonstrable in the present study. Statistical significance of the observed analgesic effects was partly obscured by the robust measures of efficacy (average changes over entire observation period) and the stringent corrections for multiple comparisons. Although 200 mg of ibuprofen is analgetic (e.g. in sore throat [20]), this dosage is still low. In tension-type headache, we have only found studies of higher dosages of ibuprofen showing a clear analgesic effect [14, 15].

This study demonstrated clear and comparable analgesic effects of ketoprofen 25 mg and 50 mg in headache compatible with episodic tension-type headache. This

could indicate that ketoprofen has a 'ceiling' effect at about 25 mg in this type of pain, similar to post partum pain [5, 6]. In other pain models, however, ketoprofen 100 mg was more effective than 25 mg [3, 6, 7]. Self-medication for ordinary headache can be started at 25 mg or possibly less, considering that half of all adverse events occurred with ketoprofen 50 mg. The present study showed the practicality of electronic diaries in the home-monitoring of 'over-the-counter' drugs. They can be an important new attribute in the development of self-medicated agents.

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